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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,743	04/15/2004	David Edwin Thurston	065435-9035	7033

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MICHAEL BEST & FRIEDRICH, LLP
ONE SOUTH PINCKNEY STREET
P O BOX 1806
MADISON, WI 53701

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,743	THURSTON ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-46* is/are pending in the application.

4a) Of the above claim(s) *26-35 and 41-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-40* is/are rejected.

7)☒ Claim(s) *36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Please note: There is a change in examiner handling prosecution in this case from Janet Coppins to Jon Epperson (AU 1639).

1. Applicants response filed May 8, 2006 is acknowledged. The following office action is hereby made non-final in view of the newly cited rejections that were not necessitated by Applicants' amendments.

Status of the Claims

2. Claims 26-46 were pending.

3. Applicant's response to the Restriction and/or Election of Species requirements is acknowledged (Applicant elected ***without traverse*** Group II, claims 36-40) and claims 26-35 and 41-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (e.g., see 5/8/06 Response, page 1).

4. Please note: Applicant's *specifically* elected species (i.e., formula 60 of figure 12) was searched and was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. See MPEP § 803.02.

5. Therefore, claims 36-40 are examined on the merits in this action.

Withdrawn Rejections

6. All previous rejections and/or objections are hereby withdrawn in view of Applicants' arguments.

New Rejections & Objections

Objections to Specification

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed (i.e., "A collection of compounds" doesn't distinguish this library from any other). Please be as specific as possible when amending (e.g., use formula (I)).

Objections to the claims

8. Claim 36 is objected to because of the following informalities:

A. Claim 36 mistakenly uses both "," and a ";" after O in line 3 (i.e., X' is CO, NH, S or O,;). Correction is requested.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For ***claim 36***, the phrase "and there is optionally a double bond between C1 and C2 or C2 and C3" is vague and indefinite because it is unclear which carbons are being referring to? Neither formula (I) nor any of the side groups for R_2 and R_3 "number" their carbon atoms as C1, C2, C3, etc. Applicants are requested to clarify and/or correct. Therefore, claim 36 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. For ***claim 36***, the phrase "R_9 (if not H-$(T)_n$-X'-Y-A)" in line 11 is vague and indefinite because it implies that R_9 could be H-$(T)_n$-X'-Y'A. However, only R_2, R_3, R_6, R_7 and R_8 have been defined in this fashion (e.g., see line 2 of claim 35 wherein R_9 is missing from this definition). Applicants are requested to clarify and/or correct. Therefore, claim 36 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 36-40 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description

rejection.

Applicants' claims are directed to a broad genus of compound libraries described by formula (I). An infinite number of libraries fall within the scope of the present claims because Applicants do not set forth any structural limitations for the "T" variables (i.e., the combinatorial units) at positions R_2, R_3, R_6, R_7 and R_8 (see also 35 U.S.C. § 112, second paragraph rejection above where the scope of R_9 was shown to be ambiguous). In addition, no upper limit is placed on the "n" variable (i.e., $n \rightarrow \infty$). That is, Applicants do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the T-groups. Likewise, dependent claims 37 and 38 similarly fail to limit both n and T. T is also left undefined for dependent claims 39 and 40.

In contrast, Applicants' specification provides only a handful of examples with very limited substitutions at the R_7 and R_8 positions such as alkyl, halo, ester, peptide (e.g., see Examples; see also figure 1, compound 7, showing "I" at position R_7 and "H" everywhere else; see also figure 2, compound 12, showing OMe at positions 6 and 7 and "H" everywhere else; see also figure 9, compound 30 wherein an alkyl amine replaces one of the methyl groups in compound 12; see also figure 10, compound 39 wherein a propenyl ester replaces one of the methyl groups in compound 12; see also figure 11, compound 50 wherein an Fmoc group replaces one of the methyl groups in compound 12; see also figure 12, compound 59 wherein a small glycine peptide replaces one of the methyl groups in compound 12). Furthermore, the R_2, R_3, R_6 and R_9 positions contain only hydrogen (e.g., see figures 1-12).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). In the present case, Applicants describe only a handful of species (e.g., see above). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous (see above). Virtually every class and subclass of molecules would fall within this claimed scope (e.g., biological polymers like peptides, non biological polymers like polyvinyl chloride, inorganic complexes, siloxanes, buckballs, etc. all fall within the scope of a "combinatorial" unit because any chemical group can be used in combinatorial synthesis).

Factors to be considered in determining whether there is sufficient evidence of possession include "**[1]** the level of skill and knowledge in the art, **[2]** partial structure, **[3]** physical and/or chemical properties, **[4]** functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the **[5]** method of making the claimed invention" (e.g., see MPEP § 2163). Here, the level of skill in the art is high, but only with regard to a few of the species (e.g., peptides). For example,

Lauf et al. state, "The preparation of new materials with novel and useful chemical and/or physical properties is at best unpredictable considering current levels of understanding. Consequently, the discovery of new materials depends largely on the ability to synthesize and analyze new compounds. Given approximately 100 elements in the periodic table, which can be used to make compositions consisting of three, four, five, six or more elements, the universe of possible new compounds remains largely unexplored" (e.g., see U.S. Patent Application Pub. No. 2004/0062911 A1, page 1, paragraph 4). Here, Applicants' claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the T groups and, as a result, would read on the "largely unexplored" universe set forth in Lauf. In addition, Applicants provide no "partial structure" or "physicochemical properties" for the T group. Nor do Applicants set forth any structure/activity relationship for the combinatorial units. Finally, Applicants have not set forth any general method for making all of these compounds (e.g., siloxanes, fullerenes, etc.).

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed libraries especially with regard to the T-groups. It is well settled that claiming only a result (e.g., compounds with T groups having the ability to function as combinatorial units) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor (e.g., compounds with small peptides at position R_6), so that others would have no incentive thereafter to explore a field already fully dominated.

O'Reilly v. Morse, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bi et al. (Bi et al. "Building Blocks for peptide and carbamate libraries" *Bioog. & Med. Chem. Lett.* **1996**, *6(19)*, 2299-2300) (3/10/05 IDS) in view of Lescrinier et al. (Lescrinier et al. "DNA-Binding Ligands from Peptide Libraries Containing Unnatural Amino Acids" *Chem. Eur. J.* **1998**, *4(3)*, 425-433) (3/10/05 IDS) and Leber et al. (Leber et al. "A Revised Structure for Sibiromycin" J.

Am. Chem. Soc. 1988, 110, 2992-2993) (3/10/05 IDS) and Suggs et al. (Suggs et al., "Synthesis and Structure of Anthramycin Analogs via Hydride Reduction of Dilactams" *Tet. Lett.* **1985**, *26(40)*, 4871-4874) (3/10/05 IDS) and Gordon et al. (Gordon et al., "Application of Combinatorial Technologies to Drug Discovery. II." *J. Med. Chem.* **1994**, *37(10)*, 1385-1401) and Gallop et al. (Gallop et al., "Applications of Combinatorial Technologies to Drug Discovery. I." *J. Med. Chem.* **1994**, *37(9)*, 1233-1251).

For ***claims 36 and 37***, Bi et al. (see entire document) teach building blocks for peptide and carbamate libraries (e.g., see abstract), which reads (in part) on the current invention. For example, Bi et al. disclose the same tricyclic ring system (e.g., see Bi et al., compound 6 wherein a dihydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine is disclosed). Bi et al. also disclose "hydrogen" at positions R_3 and R_{6-9} positions and a "carbonyl" at position C_5 (e.g., see compound 6) that falls within the scope of the current claims.

The prior art teachings of Bi et al. differ from the claimed invention as follows:

For ***claims 36-40***, Bi et al. fail to teach a C-S, C-O or C-NH bond at the C_{11} position. Bi et al. only teach the use of C=O (e.g., see Bi et al., page 2299, compound 6). Bi et al. also fail to teach the use of a solid support at the N_{10} position or a "combinatorial" unit at R_2 or the actual formation of a combinatorial library (i.e., a collection of compounds).

However, the combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. teach the following limitations that are deficient in Bi et al.:

For ***claims 36 and 37***, the combined references of Lescrinier et al., Leber et al.,

Suggs et al., Gordon et al., and Gallop et al. (see entire document) teach the incorporation of unnatural amino acids, like the unnatural amino acid disclosed by Bi, into a peptide library bound to a solid support (e.g., see Lescrinier et al., abstract; see also scheme 1 and Table 1). Incorporation of benzodiazepine "unnatural" amino acids as disclosed by Bi et al. into the DNA-binding peptide library as disclosed by Lescrinier et al. would result in the requisite substitutions at the N10 and R_2 positions (e.g., i.e., a solid support with a linking group and "combinatorial" natural or unnatural peptide unit, respectively). The combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. also teach the use of OH, OCH_3 and SPh groups at the C11 position (e.g., see Leber et al., compounds 3 and 4; see also page 2992, column 1, paragraph 1; see also Suggs et al., page 4871, last paragraph; see also scheme on bottom of page 4872 showing facile conversion of the "dione" using $NaBH_4$ in the first step), which fall within the scope of the current claims.

For ***claim 38***, the combined references of Lescrinier et al., Leber et al., Suggs et al., Gordon et al., and Gallop et al. disclose the formation of a peptide bond (once the unnatural amino acid disclosed by Bi et al. is incorporated into the library), which reads on A = NH, Y is the divalent -C(=O)-CH_2- portion of the adjacent amino acid, X' is the NH portion of the adjacent amino acid and T is the remainder of the peptide (e.g., see Lescrinier et al., page 426, Table 1 wherein any of the disclosed amino acids C-terminus amino acids can be replaced by the unnatural benzodiazepine skeleton; note also that any other peptide library could also be used and screened).

For ***claims 39 and 40***, the combined references of Lescrinier et al., Leber et al.,

Suggs et al., Gordon et al., and Gallop et al. disclose, for example, compound 1 (e.g., see Lescrinier et al., Table 1) wherein substation of the Alanine would provide n = 4). In this scenario, amino acid number 1 = the unnatural benzodiazepine, amino acid number 2 forms the A-Y-X' as set forth above and amino acids numbers 3-6 represent the four combinatorial units.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the benzodiazepine "unnatural" amino acid disclosed by Bi et al. into the DNA-Binding peptide library disclosed by Lescrinier et al. to replace any one of the natural or unnatural amino acids set forth therein because Bi et al. explicitly state that these unnatural amino acids should be used for combinatorial synthesis (e.g., see Bi et al., page 2299, We report here the synthesis of ... benzodiazepine pharmacophore for use in the synthesis of peptide ... combinatorial libraries"), which would encompass the combinatorial libraries disclosed by Lescrinier. Furthermore, a person of skill in the art would have been motivated to use the unnatural amino acids disclosed by Bi et al. because, according to Bi et al., "Amino acids that incorporate pharmacophores are particularly attractive for the synthesis of combinatorial libraries ... [and] benzodiazepine skeleton has been found [to possess] ... a wide range of biological[ly] acitv[ity]" (e.g., see Bi et al., page 2299, paragraph 1). In addition, the tricyclic pyrrolo[1,4]benzodiazepine group is known to possess DNA-binding activity (e.g., see Suggs et al., page 4871, paragraph 1, "The pyrrolo[1,4]benzodiazepine group ... is one of the most interesting classes of DNA-binding drugs"; see also Leber et al., page 2992, column 1, paragraph 1), which is exactly what Lescrinier is screening for (e.g., see

Lescrinier et al., abstract, "An unnatural peptide-based library, bound on a solid support was screened for double-stranded-DNA (dsDNA)-binding ligands." Furthermore, a person of skill in the art would reasonably have expected to be successful because benzodiazepine skeleton has been previously used in a "combinatorial format" (e.g., see Bi et al., page 2299, paragraph 1; for more support see also Gordon et al., figure 17; see also Gallop et al., page 1240, section c, establishing high skill level for peptide libraries). In addition, Lescrinier et al. teach that "unnatural" amino acids (like the one disclosed by Bi et al.) can be easily incorporated into a peptide library (e.g., see Lescrinier et al., Results and Discussion). Finally, Suggs et al. teach a facile synthesis for converting the "dione" skeleton into the OH or SPh groups using simple NaBH4 reduction (e.g., see Suggs et al., scheme on bottom of page 4872).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
January 3, 2007

JON EPPERSON
PRIMARY EXAMINER